## REMARKS

Applicants amended claim 50. Claims 52-54 and 58-59 were previously presented. Claims 1-49, 51, 56-57, and 60-65 were previously cancelled. No new matter was added. Claims 50, 52-55, 58-59 are presented for examination.

### 35 U.S.C. § 112

The Examiner rejected claims 50, 52-55, and 59 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, allegedly because the specification provides no disclosure of the structural features of modified toxins. While Applicants respectfully disagree with the Examiner's position, because a person of ordinary skill in the art would readily understand what is meant by Applicants' claimed modified toxins, Applicants have nonetheless amended claim 50 to delete "a modified toxin", "a modified diphtheria toxin", and "a modified ricin toxin", solely to expedite prosecution. As amended, claims 50, 52-55, and 59 obviate the rejection of these claims under 35 U.S.C. § 112, first paragraph. Accordingly, Applicants respectfully request that the rejection of claims 50, 52-55, and 59 under 35 U.S.C. § 112 be reconsidered and withdrawn.

### 35 U.S.C. § 103

The Examiner rejected claims 50, 52-55, and 58-59 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,171,217 ("March"), U.S. Patent No. 5,413,797 ("Khan"), U.S. Patent No. 4,919,939 ("Baker"), U.S. Patent No. 4,233,968 ("Shaw"), and U.S. Patent No. 4,942,184 ("Haugwitz"). Claim 50 is the only independent claim, and recites a method for reducing restenosis following a vascular surgical procedure, including locally administering to a human a biocompatible, non-biodegradable sustained release dosage form including a cytostatic amount of a therapeutic agent dispersed in a polymer matrix. The cytostatic amount of the therapeutic agent inhibits a vascular smooth muscle cell activity without killing the cell. The therapeutic agent is a TGF-beta production or activation stimulator, TGF-beta, tamoxifen, a nuclear enzyme DNA topoisomerase II inhibitor, a DNA polymerase inhibitor, an RNA

polymerase inhibitor, an adenyl guanyl cyclase inhibitor, a superoxide dismutase inhibitor, a terminal deoxynucleotidyl-transferase, a reverse transcriptase, lovastatin, vinblastin, cytochalasins, taxol, taxotere, trichothecene, *Pseudomonas exotoxin*, a chemotactic factor inhibitor, a chemotactic factor receptor inhibitor, an intracellular cytoskeletal protein inhibitor, a caffeic acid derivative, nilvadipine, a steroid hormone, sphingosine, somatostatin, or N-ethylmaleimide.

None of March, Khan, Baker, Shaw, or Haugwitz, disclose or suggest the subject matter recited by the claims. Instead, March discloses a method for delivering a drug to an affected intramural site for sustained release in conjunction with or following balloon catheter procedures. (See, e.g., March, Abstract). The drug is carried by microparticles of a physiologically-compatible biodegradable polymer and is injected under direct pressure into the wall of a body vessel in the region of the affected site. (See, e.g., March, Abstract). While March discloses numerous smooth-muscle cell inhibitors (see, e.g., March, col. 3, line 34 – col. 4, line 8), March does not disclose or suggest Applicants' claimed therapeutic agents. March also does not disclose locally administering a cytostatic amount of a therapeutic agent that inhibits a vascular smooth muscle cell activity without killing the cell, as Applicants claim.

None of Khan, Baker, Shaw, or Haugwitz cure March's deficiency. Khan discloses microspheres containing a specific compound – adrenocorticotropic hormone – that is used for its anti-inflammatory and immunosuppressant properties in treating multiple sclerosis, rheumatic disorders, ulcerative colitis, infantile spasms, or systemic Lupus Erythematous. (See, e.g., Khan, col. 1, lines 26-34). Baker discloses a controlled release drug delivery system for placement in the periodontal pocket, gingival sulcus, tooth socket, wound or other cavity within the mouth. (See, e.g., Baker, Abstract). Baker is wholly unrelated to inhibition of smooth muscle cells, as he discloses that his active agent may be chosen from antiseptics, antibiotics, anti-inflammatories, local anaesthetics, *tissue growth promoters*, and *tissue destruction inhibitors*. (See, e.g., Baker, col. 3, lines 36-39). Shaw discloses an intrauterine device including a cavity, the cavity includes an antifertility and antiproteolytic drug selected from aromatic monoamidines, aromatic diamidines, and non-aromatic diamidines. (See, e.g., Shaw, Abstract).

And while Haugwitz discloses taxol derivatives (see, e.g., Haugwitz, abstract), he is focused on the cytotoxic uses for taxol. For example, Haugwitz discloses that taxol is highly cytotoxic, and that his compositions provide taxol derivatives with improved water solubility while retaining the cytotoxic properties of the parent compound. (See, e.g., Haugwitz, col. 1, lines 19-21 and 33-36).

A person of ordinary skill in the art, upon reading March, Khan, Baker, Shaw, and Haugwitz, would not have found it obvious to combine their teachings to arrive at Applicants' claimed methods for reducing restenosis following a vascular surgical procedure, including using the claimed therapeutic agents at an amount that inhibits a vascular smooth muscle cell activity without killing the cell. As discussed above, none of March, Khan, Baker, Shaw, or Haugwitz, disclose or suggest the subject matter covered by the claims. While March discloses methods for delivering microparticles including certain smooth-muscle cell inhibitors to intramural sites in a blood vessel, March does not disclose or suggest Applicants' claimed therapeutic agents, nor local administration of a cytostatic amount of a therapeutic agent that inhibits a vascular smooth muscle cell activity without killing the cell, as Applicants claim. A person of ordinary skill in the art would not look to Khan, Baker, Shaw, and Haugwitz to satisfy March's deficiency, as they are wholly unrelated to Applicants' claimed methods of reducing restenosis. Khan, Baker, Shaw, and Haugwitz are instead directed to adrenocorticotropic hormone compositions, compositions for oral indications, intrauterine devices, or taxol compositions useful for their highly cytotoxic properties. Indeed, upon reading Haugwitz, a person of ordinary skill in the art would have no reason to believe that taxol could even be used in a cytostatic manner, as Applicants claim.

Furthermore, even if the teachings of March, Khan, Baker, Shaw, and Haugwitz were somehow to be properly combined, which the Examiner asserts but which Applicants do not concede, the resulting method still would not be Applicants' claimed method, at least because the resulting method still would not require locally administering a cytostatic amount of a therapeutic agent that inhibits a vascular smooth muscle cell activity without killing the cell.

Neither March, Khan, Baker, Shaw, nor Haugwitz, alone or in combination, teaches or suggests the subject matter covered by Applicants' claims. It would not have been obvious to a person of ordinary skill in the art to combine the teachings of March, Khan, Baker, Shaw, and Haugwitz, and even if the references can be properly combined, which Applicants do not concede, the resulting medical device still would not be the subject matter recited by Applicants' claims. Accordingly, for all the reasons above, Applicants respectfully request that the rejection of claims 50, 52-55, and 58-59 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Applicants believe the claims are in condition for allowance, which action is respectfully requested.

The fee for extension of time in the amount of $1110 is being paid concurrently on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 10527-1108006.

Respectfully submitted,

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/Juan Zheng/
Juan Zheng
Reg. No. 63,514

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (877) 769-7945